

The University of Chicago

STUDIES ON THE PHYSIOLOGY OF THE PANCREAS

I. A STUDY OF THE METABOLIC ACTIVITY
OF THE PANCREAS

II. A STUDY OF THE RELATION OF PANCREATIC
DUCT PRESSURE TO THE RATE OF BLOOD
FLOW THROUGH THE PANCREAS

A DISSERTATION SUBMITTED TO THE
FACULTY OF THE DIVISION OF THE
BIOLOGICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY

1933

By

ARTHUR LAWRENCE BENNETT

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A STUDY OF THE METABOLIC ACTIVITY OF THE PANCREAS

One of us (E. U. S.) has been interested in the problem of the isolation of, and the study of the physiological and chemical properties of pancreatic secretin. He has been able to make a preparation of relatively high purity. This material will, in minute doses, cause an abundant secretion of pancreatic juice and a small secretion of bile without provoking any other physiological changes known to him. The opportunity was then afforded to study the gaseous exchange, energy consumption, and ionic equilibria in the pancreas under conditions of rest and activity. Since the pancreatic juice is unlike most other body fluids in chemical composition and since the mode of stimulation is hormonal, we hoped to throw some light upon the mechanism of its secretion.

Since there are only a few published papers to which one may refer for comparisons of results or to supply lacking data, we shall omit a separate review of the literature.

The experiments represented in this paper, unless otherwise stated, were of one general plan. The rate of blood flow through the pancreas was measured. The arterial and venous pancreatic blood and pancreatic juice were collected and analyzed for various constituents. The results of these analyses and the interpretation of them furnish the basis of this paper.

METHODS. A. *Preparation of animals.* Dogs of 12 to 18 kgm. weight were used. They were fasted for 18 to 24 hours and anesthetized with barbital-Na, amytal-Na or chloralose. The abdomen was opened and the entire pancreas separated from the duodenum by a continuous row of small ligatures. Care was taken to injure neither the pancreatico-duodenal vein nor the branches from the pancreas to it. The inferior pancreatico-duodenal vein near the head of the pancreas was ligated. All branches draining into the pancreatico-duodenal vein which were not of pancreatic origin were ligated. The blood flow measured in the pancreatico-duodenal vein represented only pancreatic blood. A tight rubber ligature was placed

around the pancreas just above where the pancreatico-duodenal vein leaves the pancreas. Thus we were able to measure or collect all of the blood and juice from the known portion of the gland. The femoral artery was cannulated for taking samples of blood. The saphenous vein was cannulated and connected to a constant injection apparatus. All accessory ducts were ligated. The pancreatic duct was cannulated for the collection of pancreatic juice. At this point the animal was carefully examined and all bleeders tied. Then 20 mgm. per kgm. of heparin were injected intravenously and the same amount injected per hour by means of the constant injection apparatus into the saphenous vein.

The inlet tube of the stromuhr was then quickly connected to the pancreatico-duodenal vein for measuring the rate of blood flow. In our experience this was completed within three minutes so that the gland was not exposed to asphyxial conditions for a significant period of time. Following the operative procedure, about an hour was allowed to elapse before the experiment was started in order that any asphyxial effects upon the pancreas would be dissipated.

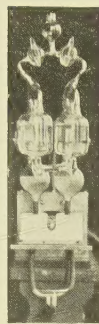
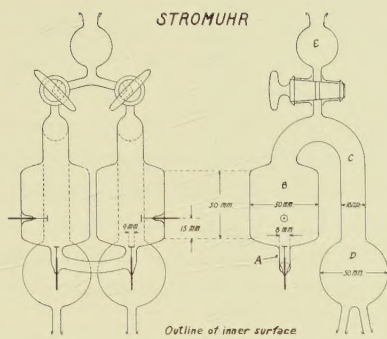
B. Measurement of blood flow. Bennett and Still (1933) constructed the blood flow apparatus especially for this study. It possesses the following advantages: 1. The back pressure is so small (less than 6 mm. H₂O) that it may be used on the venous side of an organ, thereby leaving the vasomotor nerves on the arteries intact. 2. It is automatic and simple to operate and maintain. 3. It is very accurate. Figure 1 shows the construction details of the apparatus together with the device for drawing samples of blood.

This apparatus was constructed using certain of the principles found in the stromuhrs described by Pavlov (1887), Montgomery and Lipscomb (1929), and Hemingway (1931). It has been described in detail in this paper because we believe the improvements we have made enable one to measure the rate of the blood flow with greater accuracy and less mechanical trouble than has heretofore been possible.

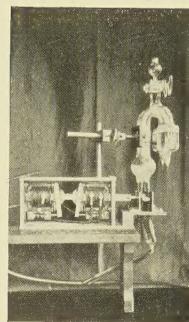
The apparatus shown in figure 1 consists of three separate parts: 1, the

Fig. 1. The structural detail of the stromuhr, valve and operating circuits:

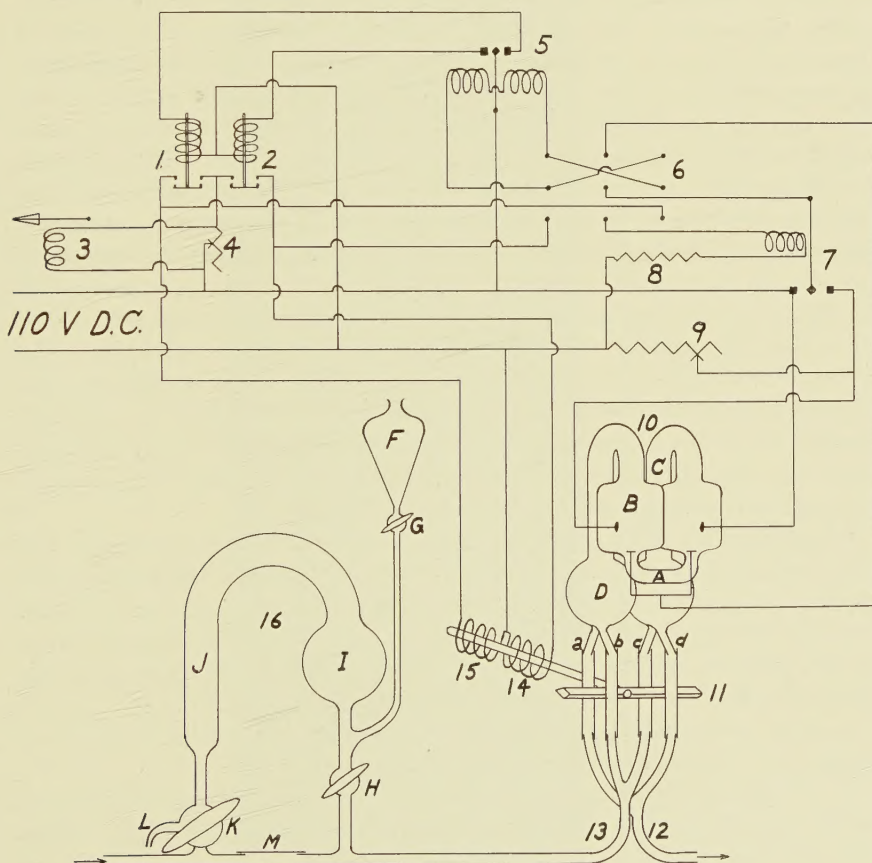
1, power relay; 2, power relay; 3, signal magnet; 4, 3000 ohm rheostat; 5, polar relay (1200 ohm); 6, T.P.D.T. switch; 7, 800 ohm relay; 8, 2000 ohm resistance; 9, 15,000 ohm rheostat; 10, stromuhr: A, chloroform chamber; B, copper sulphate chamber; C, oil chamber; D, blood chamber; E, filling chamber; 11, valve bar; 12, stromuhr outlet; 13, stromuhr inlet; 14, push solenoid; 15, pull solenoid; 16, blood sample tube; F, Ringer's reservoir; G, one way stopcock; H, one way stopcock; I, oil chamber; J, blood chamber; K, two way stopcock, $\frac{1}{4}$ inch bore; L, sample outlet; M, position of pinch clamp; 17, front view of stromuhr and valve; 18, side view of stromuhr and valve, showing valve construction and relationships of the tubes leading from the stromuhr to the animal.



17



18



sampling device (16); 2, the stromuhr and operating valve, and 3, the relays, which operate the solenoids of the valve. The stromuhr is filled as follows: The cross arm *A* is filled with CHCl_3 level with the lower electrodes, then as much extra CHCl_3 is added as is desired per volume-shift. We found it desirable to adjust the volume-shift to $\frac{1}{3}$ or $\frac{1}{4}$ of the rate of flow per minute. Then each chamber *B* is $\frac{3}{4}$ filled with a saturated CuSO_4 solution saturated with CHCl_3 . The balls *D* are half filled with heparinized saline solution. The remaining space in *B*, *C* and *D* is then filled with a low viscosity mineral oil. Balls *D*, rubber tubes from *a*, *b*, *c* and *d*, glass tubing 12 and 13 and rubber tubing leading to the venous cannulae are coated with melted vaseline.

The operation of the stromuhr: The diagram shows that the solenoids 14 and 15 are controlled through power relays 1 and 2 which in turn are operated by polar relay 5. Polar relay 5 is operated by two sets of electrodes contained in the stromuhr chambers (*A* and *B*). If solenoid 14 (push) is functioning, the valve bar 11 will compress the rubber tubes leading from *b* and *d* so that the blood will enter the stromuhr through *c* and leave through *a*. The blood entering *D* will displace chloroform in *A* until one of the electrodes in *A* is exposed to the CuSO_4 solution. This activates the polar relay 5 and in turn opens solenoid 14 and closes solenoid 15, so that the direction of flow of blood in the stromuhr is reversed. Switch 6 reverses the polarity of the electrodes to prevent deplating the electrodes and should be reversed every 4 to 6 hours. Relay 7 prevents gassing at the electrodes by disconnecting the current from the actuated side of the stromuhr and applying it to the side which will next be actuated. The figure shows structural details of the apparatus. This equipment has measured the blood flow in our experiments with great accuracy. Except in cases where the change in rate is enormous (over 300 per cent), the error has been under 0.5 per cent which, in a problem such as the one presented here, is not the largest error encountered.

Suggestions for filling stromuhr: 1. The stromuhr is clamped in an up-side down position and the chloroform admitted through the bottom, the upper stopcocks being closed. This enables one to introduce a more accurate volume of chloroform into chamber *A*. Place the stromuhr in an upright position, rotating it in such a manner that all of the chloroform will drain into chamber *A*, then attach the rubber tubes to the balls *D*.

2. After connecting the stromuhr to the valve, by suction on *E*, draw melted wax into the balls *D* to leave a thin coating.

3. In a similar fashion, draw the copper solution up through tube *C* permitting enough to flow over into chamber *B* so that it is $\frac{3}{4}$ filled. Then allow the copper solution in tube *C* to be discharged.

4. Open both stopcocks and under pressure fill both chambers *C* with saline solution almost up to the bend. Then clamp tubes to one ball and

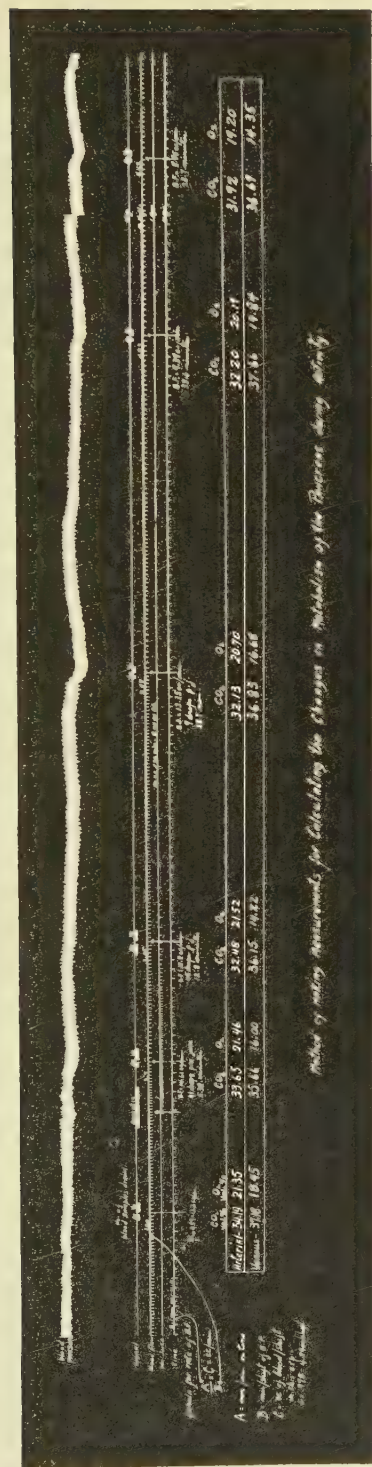


Fig. 2. A record taken from an experiment which illustrates the method of making measurements for calculating the changes in the metabolism of the pancreas.

close the stopcock on the same side. Fill *E* with oil and by permitting the saline to run out the oil will be drawn in. This is repeated until the entire chamber, with the exception of $\frac{1}{2}$ of the balls and tubes connected to them, is filled with oil. The tubes and the lower half of the balls are filled with saline solution.

The sampling device is represented by (16). Stopcock has 6 mm. bore. With stopcocks *K* and *H* closed, the blood from the pancreas passes directly into the tubes leading to the stromuhr. To take sample: open stopcock *K* and *H* and place clamp on rubber tube at *M*. Blood enters *J* forcing oil into *I* and an equivalent volume of Ringer's solution flows through *H* and thence through the stromuhr. When sufficient blood has entered *J*, remove clamp at *M* and close stopcocks *K* and *H*. To remove blood sample: adjust stopcock *K* to connect *J* and *L*; dip *L* into a receiving tube under oil; open stopcock *G* which permits Ringer's solution to enter *I* and force oil and blood out through *L*. The blood is then under oil and may be manipulated in any way desirable. It has not been exposed to the atmosphere at any time.

Figure 2 shows a record taken from an experiment and illustrates the method of making calculations.

The method of calculating the rate of blood flow from the data was as follows: The expression $\frac{A}{B} \times C = \text{cc. per minute}$ when *A* = mm. per minute on the time record; *B* = mm. per shift on the blood flow record; *C* = cc. of blood per shift. The rate at the time of the samples A7 and V7 on figure 2 was calculated from these figures: 1 minute = 8.1 mm.; 1 shift of blood = 3.00 mm.; volume per shift = 4.89 cc. Thus the rate of flow at the time was 13.2 cc. of blood per minute.

C. The CO₂ and O₂ of the blood and pancreatic juice were determined by the method of Van Slyke and Neill (1924).

D. Water content of blood, juice or tissue was determined by heating to constant weight at 105°C.

E. Glucose was determined upon zinc filtrates by the method of Shaffer and Hartman (1921).

F. Lactic acid was determined using the procedure of Friedman and Graeser (1933).

G. Glycogen was determined by the procedure described by M. Sahyun (1931).

H. The secretin used in these experiments was from one sample prepared by one of us (E. U. S.) by a method similar to that described by him, and further purified by a method involving the use of picric acid, flavianic acid, and liquid ammonia which will be described in a separate paper.

I. Precautions in handling the samples of blood: cyanide, fluoride and the ice bath were used to minimize changes in the shed blood. Samples of

blood and sera were kept in an ice bath in tonometers over mercury pending analysis.

EXPERIMENTAL RESULTS. The gaseous exchange of the pancreas under conditions of rest and hormonal stimulation.

a. *Control experiments.* It was noted in some of our first experiments that the withdrawal of samples of blood caused a progressive fall in blood pressure and in the rate of blood flow through the pancreas. Although this occurred in only part of the experiments it was felt that control experiments should be carried out in which five or more samples each of arterial and venous blood were drawn without the injection of secretin. Three such control experiments were carried out. Figure 3 shows the results of one control experiment. The results indicate that unless the blood flow is diminished by more than 50 per cent there will be no important

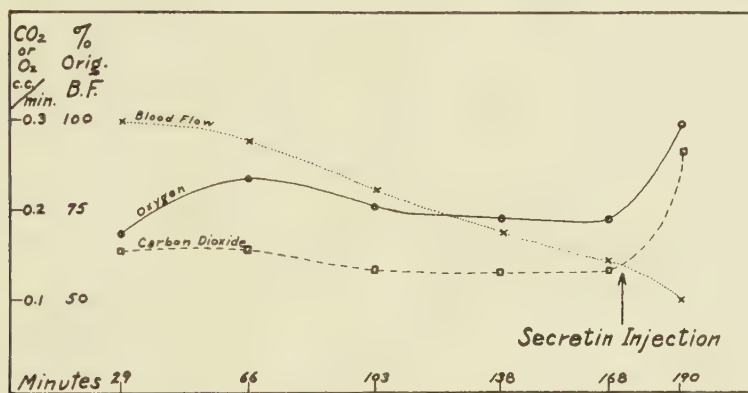


Fig. 3. Control experiment showing that a reduction in the rate of blood flow through the pancreas is without effect upon the rate of metabolism of the gland.

effect upon the rates of oxygen consumption and carbon dioxide output by the gland. As a matter of fact, we have several experiments in which the rate of blood flow through the pancreas has decreased as much as 50 per cent or more without materially influencing the rate of gaseous exchange of the gland. It would seem, therefore, that the rate of blood flow through the pancreas only bears a relation to the rate of metabolism in so far as asphyxia will develop from too slow circulation. This indicates that the pancreas is not nearly so susceptible to reduced oxygen tension as are some of the other glands of the body; e.g., submaxillary. In 2 or 3 of our experiments (data not included in this paper) the rate of blood flow diminished during the experiment to $\frac{1}{4}$ or $\frac{1}{5}$ of the control values. However, the rate of gaseous exchange was not materially affected. This was particularly interesting to us because in some cases when the blood was flowing very slowly the oxygen content of the venous blood was found to be as low as

$\frac{1}{5}$ of that of the arterial value. It should be stated, however, that none of the data reported in this paper have been drawn from experiments in which there have been such marked changes in the rate of blood flow.

b. *Effect of a single injection of secretin.* These experiments were carried out as in the control group except that after taking two control samples of blood a single injection of secretin was made intravenously. Samples of blood were taken during secretion and continued until the gland was again in the resting state, as indicated by the return of its metabolism to normal. Figure 4 shows the results of one typical experiment.

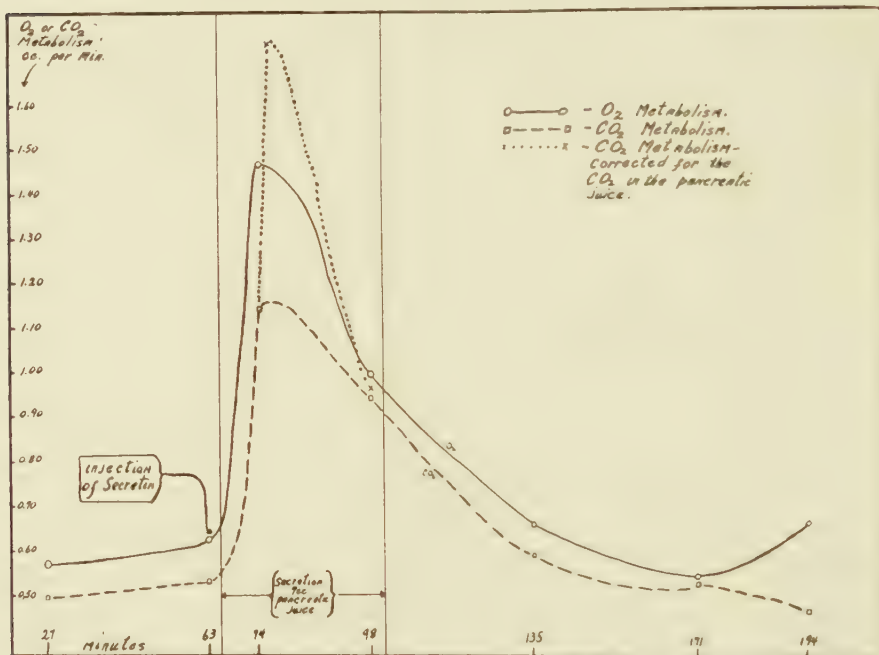


Fig. 4. The effect of a single injection of secretin on the gaseous metabolism of the pancreas.

The procedure was then modified to enable us to more clearly define the oxygen consumption and CO₂ production curves, by drawing more frequent samples of blood during the period of activity. It was observed that for a short time after the beginning of secretion, the venous CO₂ was diminished to values approaching those of the arterial blood. Table 1 shows the data and calculations from one such experiment. In this particular experiment, due to the extremely good condition of the animal, we were able to continue the work and complete two experiments. Although this experiment is similar to several others, it will be described in detail because of its completeness.

Figure 5 shows that very shortly after the injection of secretin the oxygen consumption began to rise and quickly reached a maximum. The oxygen debt was not paid until about 20 minutes after the secretion had stopped. The CO_2 production curve as calculated from the A-V difference at first was decreased. After about ten minutes, however, the CO_2 output increased greatly and did not return to the control value until some time after the secretion had stopped.

In the first part of this experiment 0.2 mgm. of secretin was injected. This led to the secretion of 2.5 cc. of pancreatic juice. The extra oxygen

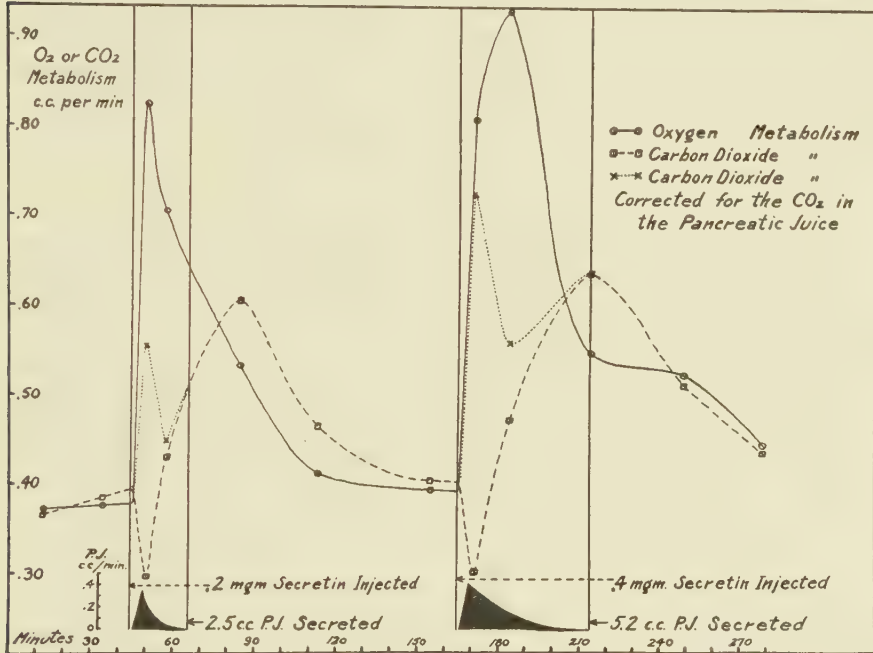


Fig. 5. The effect of a single injection of secretin on the gaseous metabolism of the pancreas.

used during the process was 10.49 cc. and the extra CO_2 produced amounted to 9.63 cc. as calculated from our data. In the second part of the experiment 0.4 mgm. of secretin was injected with the secretion of 5.2 cc. of pancreatic juice. The extra oxygen and CO_2 were 20.64 cc. and 18.04 cc., respectively. The calculated R.Q.'s for these two periods were 0.91 and 0.87.

A most interesting point seen in the experiments is the fall in A-V CO_2 difference during the first few minutes after stimulation. This was further investigated by several experiments so designed as to throw light upon the situation by drawing frequent samples of blood during the first

few minutes after the injection of secretin. In three of eight experiments the venous CO_2 actually fell to below the arterial CO_2 . The data from one of these experiments is given in table 2. In one of the experiments it

TABLE 1

The data from an experiment which show the changes in the metabolism of the pancreas following the intravenous injection of secretin

PERIOD NUM- BER	TIME OF PERIOD	TOTAL BLOOD FLOW	RATE OF BLOOD FLOW	ARTERIAL		VENOUS		RATE OF METABOLISM AT TIME OF SAMPLE		CORREC- TION FOR CO ₂ IN PAN- CREATIC JUICE	CORRECTED RATE OF METAB- OLISM AT TIME OF SAMPLE	
				CO ₂	O ₂	CO ₂	O ₂	CO ₂	O ₂		CO ₂	O ₂
				cc./ minute	cc./per cent	cc./per cent	cc./per cent	cc. minute	cc. minute		cc. min- ute	cc./min- ute
	minutes	cc.										
	0											
1	12.2	265	16.28	37.66	23.59	39.83	21.39	0.353	0.360		0.353	0.360
2	22.8	401	16.38	34.90	23.50	37.18	21.27	0.373	0.365		0.373	0.365
Injection of 0.2 mgm. secretin												
3	6.6	107	15.18	33.95	23.50	35.82	18.14	0.284	0.814	0.270	0.554	0.814
4	7.56	98	12.73	32.90	23.50	36.18	18.05	0.420	0.694	0.031	0.451	0.694
5	25.9	328	12.13	32.80	22.85	37.68	18.56	0.592	0.521		0.592	0.521
6	28.8	318	13.15	32.85	22.10	36.29	19.05	0.452	0.401		0.452	0.401
7	41.0	552	13.20	34.19	21.35	37.18	18.45	0.395	0.383		0.395	0.383
Injection of 0.4 mgm. secretin												
8	5.32	83	14.62	33.65	21.46	35.66	16.00	0.294	0.798	0.429	0.723	0.798
9	12.8	152	12.57	32.48	21.52	36.15	14.22	0.461	0.918	0.100	0.561	0.918
10	28.7	372	13.35	32.13	20.70	36.83	16.68	0.627	0.537		0.640	0.537
11	35.6	352	9.39	32.20	20.19	37.66	14.84	0.513	0.502		0.513	0.502
12	27.7	362	8.95	31.92	20.20	36.69	14.35	0.427	0.434		0.427	0.434

TABLE 2

The data from an experiment in which the CO_2 content of the venous blood fell below that of the arterial blood

TIME	ARTERIAL		VENOUS		CORRECTED FOR CO_2 IN JUICE	
	CO_2	O_2	CO_2	O_2	CO_2	O_2
	cc./per cent	cc./per cent	cc./per cent	cc./per cent	cc./min- ute	cc./min- ute
Control.....	16.65	20.65	22.90	12.51	0.150	0.200
3 minutes after secretin.....	15.61	20.18	13.04	10.14	0.580	0.439
5 minutes later.....	16.16	20.88	21.38	5.79	0.478	0.360
10 minutes later.....	16.03	18.15	23.03	6.55	0.233	0.258
1 hour later.....	16.33	17.69	23.11	8.04	0.144	0.205

almost equalled the arterial CO_2 and in the remaining four experiments it was only slightly higher than the corresponding arterial CO_2 values but lower than the resting venous values. This, of course, brings up the

fundamental question as to whether the bicarbonate of the juice is entirely metabolic in origin or whether some of it comes directly from the blood.

c. *The effect of continuous hormonal stimulation.* These experiments were of the same general character and plan as those cited under *b* except secretin was continuously injected over a period of about one hour. In this way the pancreas was maintained in a state of great activity for a relatively long period of time. It was hoped to determine if prolonged activity resulted in changes other than those already noted. Figure 6 shows graphically one of our experiments.

It will be noted that the changes in respiration resemble those due to the single injection of secretin except that they last longer. It is interesting to note that the average rate of oxygen consumption per gram of wet tissue in our studies was: Resting 0.029 cc. per gram per minute and during

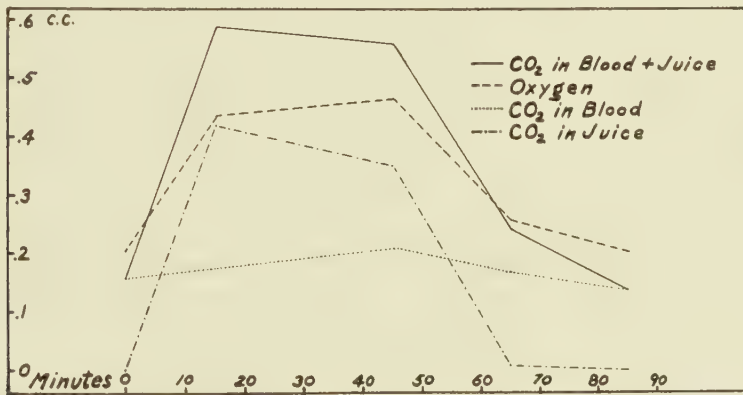


Fig. 6. The effect of continuously injecting secretin on the gaseous metabolism of the pancreas.

activity 0.062 cc. per gram per minute. Gerard and Still (1932) using the Warburg technique on excised rat's pancreas found the oxygen consumption to be 0.01 cc. per gram per minute resting and 0.014 cc. per gram per minute after the addition of secretin.

Table 3 gives the summary of eleven experiments selected because of the fact that they were completed without mishaps of any kind which would cause us to question the results. The extra R.Q. of work from these data suggests that the energy for the work of secretion comes from carbohydrate. Therefore, we planned experiments to investigate that point.

d. *Study of carbohydrate utilization by the pancreas.* The general plan of these experiments was the same as heretofore described. Larger samples of blood were taken to allow for duplicate analyses of CO₂, O₂, glucose and lactic acid. Figure 7 gives one typical experiment.

In none of our three experiments have we been able to show a quanti-

tatively consistent change in the glucose used by the gland during activity as compared with the resting state. In all of our experiments the A-V difference of glucose per minute decreased with the onset of activity. Cer-

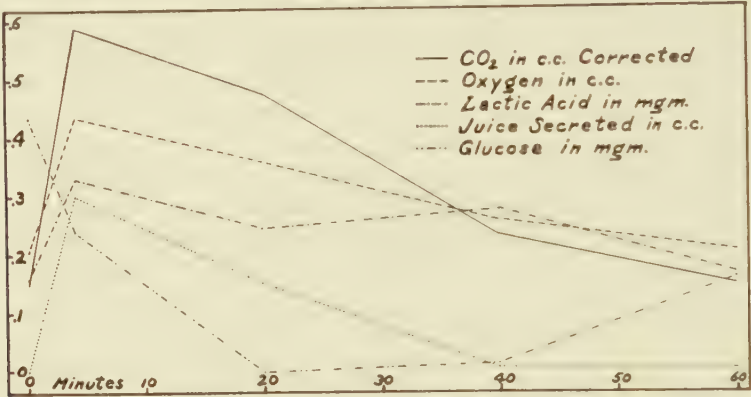


Fig. 7. The effect of secretin upon the respiration, glucose and lactic acid metabolism by the pancreas.

TABLE 3

The data from 11 experiments, showing the resting metabolism of the pancreas, and the respiratory quotient

NUMBER	RESTING CO ₂ (DRY WEIGHT)		RESTING O ₂ (DRY WEIGHT)		RESTING R.Q.	EXTRA R.Q. OF WORK
	cc./minute	cc./gram/minute	cc./minute	cc./gram/minute		
1	0.134	0.061	0.196	0.089	0.69	0.96
2	0.321	0.066	0.354	0.073	0.91	1.04
3	0.365	0.100	0.507	0.139	0.72	1.22
4	0.363	0.100	0.395	0.109	0.92	0.98
5	0.543	0.180	0.629	0.212	0.86	0.94
6	0.341	0.095	0.463	0.129	0.735	1.04
7	0.224	0.042	0.310	0.057	0.72	0.97
8	0.338	0.131	0.407	0.158	0.83	0.99
9	0.373	0.102	0.365	0.100	1.02*	0.95
10	0.395	0.109	0.383	0.105	1.03*	0.88
11	0.151	0.108	0.201	0.143	0.751	1.60
av	0.3226	0.0994	0.3827	0.1194	0.792	1.05
s.d.	±0.0351	±0.0111	±0.0380	±0.0130	±0.029	±0.061

* Not used in calculating ad.

tainly this is not evidence for a decreased utilization of glucose. Rather we believe it to represent glucose added to the venous blood by the active gland. This would diminish the A-V difference. In all of the experiments the lactic acid produced was increased as is shown in figure 7.

These findings together with the calculated R.Q. of activity (see table 3) caused us to look farther for the source of the increase in carbohydrate metabolism by the gland during activity. It seemed possible that a glycogen breakdown furnished carbohydrate for oxidation and added glucose and lactic acid to the venous blood. Four experiments were carried out to test the hypothesis: samples of the pancreas were removed before, during and after secretion. They were analyzed for glycogen. We have found as great differences in the glycogen content of adjacent parts of the resting pancreas as we have during and after activity. It seems, therefore, that the pancreas is not of uniform composition.

DISCUSSION. Probably the most interesting finding in these experiments was the diminution of the A-V difference in the CO_2 during the first stage of secretion. A consideration of the data from experiments similar to the one cited in tables 1 and 2 may elucidate somewhat the question as to the source of HCO_3 in the juice, which is a somewhat moot question. Woiner (1928) believes the CO_2 of the juice is dependent upon (and therefore arises from) the blood serum. He found that continuous secretion by the pancreas led to a lowered alkali reserve due to loss of fixed base. Hammarsten and Jorpes (1928) did not confirm Woiner. They found that continuous secretion did not lead to a diminution of the alkali reserve. They found acid to accumulate in the gland during activity. They hold that the base comes from the blood and the CO_2 from the gland. Ball (1930) from an excellent series of experiments came to the same conclusion, "since the juice bicarbonate is remarkably independent of the serum bicarbonate." The views of these workers are either partly or totally in disagreement. We might point out that, while their experiments were excellently planned and executed for the study of the total metabolism of pancreatic secretion, they were unable to express their results quantitatively with respect to time and therefore failed to observe the first phase of secretion. Our attempt to express our data quantitatively with time and to measure the rate of blood flow brought these considerations to our attention.

Since in every experiment planned to detect it, we observed the diminished A-V difference in CO_2 during the first few minutes after the injection of secretin, we are convinced as to the correctness of our observations (see table 1 and fig. 5). Probably our data entitle us to consider further the mechanism involved and the source of HCO_3 in the pancreatic juice.

Our data suggest in the resting gland there is little passage of substances other than oxygen from the blood into the gland with the exception of that which goes into the formation of lymph (which has not been directly studied). On the other hand CO_2 at least passes from the gland into the blood. With the onset of secretion the venous CO_2 becomes diminished and HCO_3 appears in the juice. After a few minutes, although the CO_2 of the juice remains high or even increases in concentration, the venous

CO_2 rises above the resting concentration. This, of course, may be interpreted as indicating that the entire CO_2 of the juice is metabolic in origin, and that more CO_2 is produced by the gland, at a given time, than is secreted in the juice, because of the raised level of the venous CO_2 during the second phase of the secretion. However, we cannot overlook the three experiments in which, during the early phase of secretion, we found the venous CO_2 lower than the arterial CO_2 (see table 2). These results cause us to lean toward the following explanation: During the first phase of secretion the juice CO_2 arises partly from the blood and partly from the metabolism of the gland. This seems to be particularly so if the pancreas has received a maximal secretin stimulation. After a continuous "secretory state" has been established the increased metabolic CO_2 of the gland is more than enough to supply the juice and, therefore, a part of it passes into the blood. Our evidence is therefore in agreement with and has contributed to the theories advanced by Hammarsten and Jorpes and Ball.

We have carried out equilibrium experiments to determine directly the change in fixed acid and base of the arterial and venous blood, before secretion, at the height of secretion, and after secretion. These experiments will be presented in another paper.

SUMMARY

A method has been described for the study of the metabolism of a gland *in situ*. The method has been applied to the pancreas with results which we feel enable us to draw the following conclusions.

1. The secretion of pancreatic juice is accompanied by an increased consumption of oxygen. A considerable oxygen debt usually develops and is usually "paid" within 30 minutes after the gland has ceased to secrete.

2. At the beginning of the secretion of juice, there is a fall in the pancreatic venous CO_2 due to the removal of much of the metabolic CO_2 of the gland by the juice. In some cases the venous CO_2 may fall below the value obtained for the arterial blood. Soon, however, the metabolic CO_2 is sufficient to supply the BHCO_3 for the juice and to increase the venous CO_2 above the resting level. We, therefore, believe the principal source of CO_2 in the juice is from the metabolism of the gland. As indicated a small portion may arise during the beginning of secretion from the blood.

3. The average resting R.Q. of the gland was found to be 0.79. We believe that figure is probably too high because it is difficult to study the gland under conditions of absolute rest. The average R.Q. of work (extra R.Q.) was found to be 1.05.

4. Whether or not carbohydrate is the source of energy during activity in the pancreas is an open question.

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A STUDY OF THE RELATION OF PANCREATIC DUCT PRESSURE TO THE RATE OF BLOOD FLOW THROUGH THE PANCREAS

Those who have concerned themselves with the mechanism involved in secretin and nerve activation of the pancreas have from the first considered the possible importance of relative changes in the rate of blood flow through the gland. It is well established that changes in the rate of blood flow through the pancreas do affect the rate of secretion. Anrep (1916) demonstrated the inhibitory effect on pancreatic secretion brought about by splanchnic stimulation or compression of the aorta. We have confirmed these findings in experiments in which we measured the blood flow and decreased it by means of hemorrhage. In one experiment a decrease in the blood flow (through the pancreas) of 57 per cent resulted in a 44 per cent reduction in the rate of pancreatic juice secretion. Likewise an increase in rate of blood flow was demonstrated to have a reverse effect, namely, to increase the rate of secretion.

Weaver, Luckhardt and Koch (1926) first prepared what was considered to be vaso-dilatin free secretin. When its action was demonstrated by Weaver (1928) the question of a possible histamine or histamine-like action of secretin seemed definitely settled in the negative. However, recently, Gayet and Guillaumie (1930) found that secretin activation of the pancreas was accompanied by an increase in the rate of blood flow. They reported an even closer correspondence between the secretory and blood flow rates when the gland was activated by nerve stimulation. More recently (1932) these investigators have performed several experiments in which they found that a preliminary decrease in the rate of blood flow accompanies secretin stimulation.

The relation of nerve activation of the pancreas to vaso-motor effects upon the gland has been difficult to determine. Francois-Frank, and Hallion (1897) observed an increased volume of the gland accompanying the secretion which was brought about by vagus stimulation and they ascribed this phenomenon to vaso-dilatation in the gland. On the basis of this finding they claimed to have demonstrated vaso-motor fibers to the pancreas in the vagi. Anrep (1915) showed that the vagi carry both

secretory and inhibitory fibers to the pancreas. After studying the effects of these two sets of fibers upon the gland he concluded that the increase in pancreatic volume resulting from vagus stimulation is due to a retention of juice either within the gland cells or within the duct system. It was his conclusion that there are neither vaso-constrictor nor vaso-dilator fibers to the pancreas in the vagi. By direct measurement of blood flow Gayet and Guillaumie (1930) have demonstrated a vaso-dilator effect in the pancreas as a result of vagus stimulation.

From time to time, we have made observations in our studies on the pancreas, which directed our interest to the relationship between blood flow and secretion. In a particular series of experiments in which we were measuring the blood flow through the pancreas (Still, Bennett and Scott, 1933), it was observed that a certain sample of secretin, would occasionally cause an increase in the rate of blood flow. On examining our data we found that if an increase in the blood flow occurred, certain other things seemed to be involved. 1. If the duct was twisted or the cannula in the pancreatic duct was obstructed by clotted pancreatic juice, the injection of secretin invariably caused an increase in the blood flow. In one case when the injection of secretin had failed to cause a flow of juice, we attempted to loosen the obstruction by injecting a small quantity of saline through the cannula. It was observed that immediately following the short period of increased duct pressure, the rate of blood flow increased markedly and continued to exceed the previous rate for a period of several minutes after the pressure was released.

By repeating this procedure on several dogs it was found that an increase in the pancreatic duct pressure caused by the injection of from 3 to 6 cc. of saline or pancreatic juice would consistently cause an increase of from 20 per cent to 233 per cent in the volume of blood flowing through the gland over an average period of 11.6 minutes after the pressure had been released. It was also observed that frequently this procedure was accompanied by a momentary pause in respiration and a slight dip or rise in carotid blood pressure. 2. If the latent period of the secretion was prolonged (probably the duct contained a loose clot or a very thick juice) the injection of secretin lead to an increased blood flow. 3. The first injection of secretin sometimes led to an increased blood flow while subsequent injections of the same secretion preparation were without effect on the blood flow. 4. When the latent period was short (about 1 minute) and the duct and cannula entirely open and free to discharge pancreatic juice, the injection of secretin caused no change in the rate of blood flow.

This led us to reëxamine the data from 50 experiments in which we had measured the rate of blood flow through the pancreas in a study of the metabolism of the gland, and to perform new experiments particularly designed to throw light upon this problem.

In these experiments dogs of 8 to 9.5 kgm. body weight were used. The anesthesia consisted of intramuscular and intravenous barbitol-Na, amy-tal-Na or chloralose.

The half of the pancreas drained by the pancreatico-duodenal vein was completely isolated from the duodenum by a continuous row of ligatures between the two organs. The pylorus was ligated as was the duodenum below the pancreas. A kymographic record was made of respiration, carotid blood pressure, blood flow through the pancreatico-duodenal vein, and pancreatic secretion. The blood flow was measured by means of the automatic stromuhr described by Bennett and Still (1933). Heparin was used as the anticoagulant.

The most significant criterion of changes in blood flow in these experiments was considered to be the per cent increase in total volume of blood passing through the gland during the period of changed rate as compared with the volume which would have gone through the gland during the same period at the previous rate of flow. This is hereafter referred to as the per cent increase in blood-flow volume.

The results suggested the possibility of a reflex vaso-dilatation with the stretching of the duct wall as the necessary stimulus. In order to determine the possibility that normal secretory pressure is sufficient to equal or exceed the stimulus threshold an analysis of fifty experiments was made. Of these fifty experiments in which blood-flow records were made during secretin activation of the gland there were ten in which for some unknown reason the cannula failed to deliver the pancreatic juice freely. Either the latent period was greater than 2.5 minutes or no juice left the gland at all. In the remaining 40 experiments the latent period was less than 2.5 minutes and the quantity of juice secreted was sufficient to be considered entirely satisfactory. Assuming that the pancreatic duct pressure was higher in the 10 experiments showing unsatisfactory elimination of juice than in the 40 experiments with relatively free egress of juice it was found that in those experiments with high duct pressure the average per cent increase in the volume of blood flowing through the gland was 40 per cent as compared with 9.4 per cent in those with low duct pressure. Also the average period of changed blood-flow rate was 20.0 minutes in the former as compared with 13.3 minutes in the latter. The secretory pressure developed with the gland itself was the only pressure involved in these experiments.

In order to measure the duct pressure which the gland developed while effecting this vaso-dilatation phenomenon two experiments were carried out. The gland developed a pressure of 18 mm. Hg the first experiment and 18.5 mm. Hg the second. The average per cent increase in volume of blood passing through the gland at 18 mm. Hg pressure was 14.2 per cent as compared with 3.3 per cent when the juice was allowed to flow freely through the cannula.

DISCUSSION. As may be seen from the table of results, it is necessary to have an increased pancreatic duct pressure for only a few seconds in order to cause an increase of 20 per cent or more in the blood-flow volume over a period of several minutes. The fact together with the magnitude of the blood-flow change and also the observation of central effects on respiration and general blood pressure leads us to believe that there is a reflex mechan-

TABLE 1
A study of the relation of pancreatic duct pressure to blood-flow through the gland

DATE	EXPERIMENT	PROCEDURE	VOLUME INJECTED INTO DUCT	PANCREATIC DUCT PRESSURE	TIME PRESSURE MAINTAINED	BLOOD-FLOW CONTROL	BLOOD-FLOW AT TIME OF MAXIMUM CHANGE	CHANGE IN RATE OF BLOOD-FLOW	TIME FOR MAXIMUM BLOOD-FLOW CHANGE	TOTAL VOLUME CHANGE IN BLOOD-FLOW	PERIOD OF CHANGED BLOOD-FLOW	PER CENT VOLUME CHANGE IN BLOOD-FLOW
			cc.	mm. Hg	min.	cc./min.	cc./min.	cc./min.	min.	cc.	min.	per cent
10/ 8/31	1	Inject in duct			24/60	3.0	15.0	12.0	1	24.0	6	133
10/ 8/31	2	Inject in duct	6		20/60	2.7	12.4	9.7	1.5	25.2	7	233
10/ 8/31	3	Inject in duct	5		1	5.0	12.4	7.4	1	17.6	9	44
10/15/31	4	Inject in duct	5		51/61	5.0	11.0	6.0	1	32.0	32	20
4/28/32	5	Intra-v, Sec.		Pressure assumed to be high because of faulty elimination of pancreatic juice		4.10	6.03	1.93	4	94.7	43	54
4/30/32	6	Intra-v, Sec.				6.24	9.23	2.99	2	25.3	12	38
5/28/32	7	Intra-v, Sec.				7.62	10.97	3.35	7	46.0	30	20
6/11/32	8	Intra-v, Sec.				1.25	3.21	1.96	6	14.4	21	55
7/ 5/32	9	Intra-v, Sec.				10.45	25.40	14.95	6	99.5	18	59
7/20/32	10	Intra-v, Sec.				5.26	7.88	2.62	7	21.7	19	22
7/30/32	11	Intra-v, Sec.				8.85	37.80	28.95	3	130.2	16	105
8/ 2/32	12	Intra-v, Sec.				16.71	19.61	2.90	7	31.2	12	18
8/17/32	13	Intra-v, Sec.				15.15	21.90	6.75	5	34.0	8	29
8/20/32	14	Inject in duct	5		7/60	1.65	2.57	0.92	1.5	3.8	10	23
3/23/33	15	Inject in duct	3		24/60	7.45	27.95	20.5	0.5	34.8	6	78
5/11/33	16	Sec., duct open			0	2.68	2.68	Normal rate of change				0
		Sec., duct closed	18		10	2.06	2.77	0.71	6	14.8	37	19.4
	17	Sec., duct open	0			2.37	2.59	0.22	2	2.2	14	6.6
		Sec., duct closed	18.5		9	2.31	2.59	0.28	2	3.75	18.2	9.0

ism involved. There remains of course the problem of determining the units of the reflex arc.

It may be that the vaso-dilator fibers which Gayet and Guillaumie claim to have demonstrated in the vagi are part at least of the motor side of this arc. Also it may be suggested that the increase in volume of the pancreas which Francois-Frank and Hallion first described is in reality a combination of the two effects, the vaso-dilatation being the direct result of distention of the gland by the accumulating juice. Likewise in the light of this

phenomenon it is easily understandable that carefully purified secretin preparations which are considered vasodilatin-free may occasionally cause quite a marked increase in blood flow when injected, simply because there is a momentary retention of juice for one reason or another. This would account for the variable results reported by Gayet and Guillaumie and also observed by the author. We, of this laboratory are thoroughly convinced that secretin may be prepared which is entirely vaso-dilatin-free. The two preparations B and 413 have shown an average increase in blood-flow volume of zero in twenty-five experiments. But in single experiments

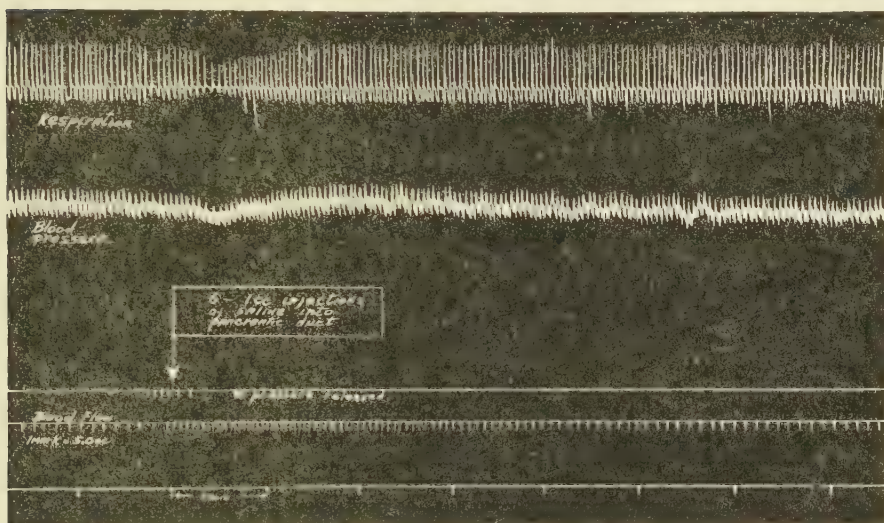


Fig. 1. A tracing showing the effect of raising the duct pressure in the pancreas by injecting saline upon the rate of blood flow through the organ.

sample B has produced as high as a 27 per cent increase in blood-flow volume.

CONCLUSIONS

1. Increased pancreatic duct pressure causes an increased rate of blood flow through the pancreas.
2. The pancreas, when secreting against an obstruction of the duct, is capable of producing pressure sufficient to cause an increase in the rate of blood flow through the glands.
3. The mechanism whereby increased pancreatic duct pressure causes an increased rate of blood flow through the pancreas is probably of the nature of a nervous reflex.

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